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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/087,142	03/01/2002	Lakshmi Rambhatle	093/005P	3039

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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/087,142	RAMBHATLE ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/10/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Amendment and Remarks, filed 6/10/04, have been entered. Claims 17-20 are added. Claims 1, 2, 13-16 are amended. Claims 1-20 are pending and under current examination.

Information Disclosure Statement

Applicants' IDS, filed 6/10/04, has been considered.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).
A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 6, 7, 9, 10, 13 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13-28 of copending Application No. 10/001,267. Although the conflicting claims are not identical, they are not patentably distinct from each other because

both sets of claims are directed to methods of differentiating pPS cells into cells that have the morphological features of hepatocytes. The instant claims are directed to methods for producing hepatocytes by culturing pPS cells in a medium containing a histone deacteylase inhibitor, and in particular embodiments, n-butyrate. The '142 claims are directed to hepatocyte cell populations and methods of producing the hepatocyte cell populations by culturing pPS cells in the presence of a hepatocyte differentiation factor, in particular n-butyrate. Accordingly, the instant claims are rendered obvious in view of the '267 claims, because they both recite the same methods of differentiating pPS cells in the presence of the same differentiating factor, n-butyrate.

Applicants acknowledge the double patenting rejection and state that upon indication of subject matter Applicants undertake to file a terminal disclaimer in this or the other application, or to take appropriate action to obviate double patenting. See Response, p. 5.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The prior rejection of claims 14-16 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 6, 23, 24, 25 of U.S. Patent No. 6,506,574 is withdrawn in view of Applicants' filing of a

terminal disclaimer over the '574 patent. The terminal disclaimer is found to be proper and is approved.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 3-20 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a substantial or specific asserted utility or a well established utility.

The claims are directed to a differentiated cell population as part of a system for obtaining hepatocyte lineage cells, wherein the system comprises a) primate pluripotent stem cells isolated from a primate blastocysts and cultured in vitro, and b) the population of differentiated cells obtained by differentiating the isolated pPS cells and wherein at least 60% of the cells in the differentiated cell population have at least three of the following characteristics: antibody-detectable expression of

AAT, absence of antibody-detectable expression of alpha-fetoprotein, RT-PCR detectable expression of ASGR, evidence of glycogen storage, evidence of cytochrome p450 activity, evidence of glucose-6-phosphatase activity and the morphological features of hepatocytes. In further embodiments, the claims are directed to using the differentiated cells of the system.

The claims fail to have a substantial or specific asserted utility because the instant specification fails to provide a utility for the system of two isolated cell populations comprising pPS cells and hepatocyte precursor cells. Although the specification contemplates various utilities for either the pPS cells, or the hepatocyte precursor cells, there is no specific or substantial utility provided by the specification for the cells in a system of two isolated cell populations. For example, the specification teaches that the invention provides a system for efficient production of primate cells that have differentiated from pluripotent stem cells into cells of the hepatocyte lineage. The specification teaches that the embryonic stem cells, originating from human blastocysts, can be differentiated into hepatocytes. See p. 4, and that the hepatocytes can then be used in methods of screening for compounds of hepatocellular toxicity or modulation. See p. 5, lines 11-17. Although the specification provides a clear utility for each of the separate cell populations, these are not specific or substantial utilities for the system of two isolated cell populations. Separate utilities are not sufficient grounds to find utility for the composition, because it is the composition that it is claimed, and the

composition that requires a patentable utility. Thus, it is determined that the claimed invention lacks a substantial and specific asserted utility.

Claims 1 and 3-20 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a substantial or specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. And the claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a system of two cell populations for generating human hepatocyte cells. As claimed, the two cell populations are intended to be used together. However, the specification fails to specifically disclose how to use these two cell populations together. The specification teaches that the embryonic stem cells, originating from human blastocysts, can be differentiated into hepatocytes. See p. 4, and that the hepatocytes can then be used in methods of screening for compounds of hepatocellular toxicity or modulation. See p. 5, lines 11-17. Further, the specification does not specifically contemplate a set of two isolated cell populations, as instantly claimed.

The specification discloses that human ES cells were maintained in an undifferentiated state in a culture essentially free of feeder cells. The specification

teaches that human ES cells were then induced to differentiate by culture using n-butyrate. The cells were then analyzed by immunocytochemistry, using antibodies against different liver specific markers. See Table 4. However, none of the working examples demonstrate the use of the claimed system of two cell populations. It is reiterated that the specification does not contemplate utilizing a system of two cell populations, as instantly claimed, and thus, the specification fails to provide adequate teachings with regard to how to use the claimed composition. Thus, there is no enabled use for the two cell populations as claimed because it is not clear how the populations would be used as instantly claimed. Although the specification provides specific uses for each of the cell populations, the specification fails to provide a specific, enabled use for the system of two cell populations.

Accordingly, in view of the lack of teachings or guidance provided by the specification with regard to an enabled use for the system of two cell populations, it would have required undue experimentation for one of skill in the art to use the claimed invention.

Claim Rejections - 35 USC § 112

The prior rejections under 112, 2nd paragraph, are withdrawn in view of Applicants' amendments to the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:
A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The prior rejection of claims 1-8 and 14-16 under 35 U.S.C. 102(b) as being anticipated by Kaneko et al. is withdrawn in view of Applicants' amendment to the claims, now reciting a system comprising two populations of cells. Applicants argue that previous to making the instant invention, there were only two principle sources of making hepatocyte-like cells, the first to separate cells from the liver tissue obtained from the whole animal, and hepatocyte-like cells obtained from cancer cells. Applicants argue that the instant invention provides an important new source of hepatocyte lineage cells for potential use in drug-screening and therapy. Applicants argue that claim 1 has been amended to distinguish the hepatocytes of the invention from prior art cells by explicitly stating the cells are part of a system. Applicants argue that claim 2 is now distinguished from the art of record, because the Kaneko reference teaches Chang liver cells, which were originally thought to be normal liver cells, but have since been shown to be established by HeLa contamination and that HeLa cells are karotypically not normal. See p. 8 of the Response.

This is found to be persuasive, in view of Applicants' arguments with regard to the karyotypic abnormality of Chang liver cells.

Claim 2 is rejected under 35 U.S.C. 102(b) as being anticipated by Chen et al. [J. Biomed. Sci., ., 5:435-440 (1998)].

Note: Applicants amendment to the claims now recite that the cell population is hepatocytes. Prior to this amendment, the claims broadly encompassed other cell types. Thus, a new rejection over this claim is found to be appropriate.

Chen teach the isolation of human liver tissues from non-tumor parts of livers from patients. See p. 436, 1st column, Cell Isolation. Further, Chen teach the isolation of hepatocytes. Seep. 436, 1st column, Culture Hepatocytes. Chen teach the growth of hepatocytes on a Matrigel matrix in a hormonally defined medium and that analysis of the cells were characteristics of hepatocytes. See p. 436, 2nd column, Growth of Heptocytes. Note that any human cell would be differentiated from pPS cells or human ES, as required by the claims. Furthermore, the claims' requirements of particular characteristics would be inherent to hepatocytes. "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties

applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Accordingly Chen anticipate the claimed invention.

Claim 2 is rejected under 35 U.S.C. 102(b) as being anticipated by Hoshi et al. [In Vitro Cell. And Dev. Bio., 23(10):723-732 (1987)].

Hoshi teach the isolation of hepatocytes from normal human fetal livers. See p. 724. As stated above, the claims are anticipated by Hoshi because they teach human hepatocytes.

Claim 2 is rejected under 35 U.S.C. 102(b) as being anticipated by Kono et al. [In Vitro Cell. And Dev. Bio., 33:467-472 (June 1997)].

Kono teach the isolation of human hepatocytes from normal human liver tissue. See Table 1 and p. 468, 2nd column. Kono teach that these hepatocytes exhibited the morphology of hepatocytes (see p. 468, 2nd column, Morphology), expressed albumin (p. 468, 2nd column, Albumin Secretion), and cytochrome p450 (p. 469, 2nd column, Cytochrome p450 associated enzyme activity). Accordingly, Kono anticipate the claimed invention.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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